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REMARKS

Claims 1-4, 8-10 and 19 were pending in the subject application. By this Amendment applicants have canceled Claims 1-4, 8-10 and 19 and have added new Claims 20-23. New Claims 20-22 correspond to canceled Claims 1-3 and new Claim 23 corresponds to canceled Claim 19. Entry of new Claims 20-23 is respectfully requested. Applicants maintain that the claims presently under examination, namely Claims 20-23, define patentable subject matter and earnestly solicit allowance of these claims.

Objection to Disclosure

The disclosure was objected to as requiring amendment to update the status of the parent application.

In response, applicants have hereinabove amended the specification to include a statement indicating the status of the parent application.

Objection to Drawings

The objections on the Notice of Draftperson's Patent Drawing Review have been noted. Applicants will prepare and submit formal drawings upon the Examiner's allowance of the claims.

35 U.S.C. §112, Second Paragraph Rejection

The Examiner rejected Claims 1-4, 8-10 and 19 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to

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particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In response, applicants have hereinabove canceled Claims 1-4, 8-10 and 19 and have added new Claims 20-23. Applicants believe new Claims 20-23 more clearly set forth and define the invention.

Accordingly, applicants respectfully request reconsideration and withdrawal of this rejection.

35 U.S.C. §103(a) Rejections of Claims 1-4, 8-10 and 19

The Examiner rejected Claim 1 under 35 U.S.C. §103(a) as being unpatentable over Olsson, et al. ("Olsson"); Claims 2, 3 and 19 under 35 U.S.C. §103(a) as being unpatentable over Olsson as applied to Claim 1 in further view of Tsuji, et al. ("Tsuji"), or Friedrich, et al. ("Friedrich"), and, if necessary, further in view of Buth, et al. ("Buth"); and Claims 4 and 8-10 under 35 U.S.C. §103(a) as being unpatentable over Olsson as applied to Claim 1 in further view of Matsuura, et al. ("Matsuura").

Applicants respectfully traverse these rejections and maintain that the pending claims are patentable over the cited references.

Regarding Olsson, the Examiner stated that it would have been obvious to one of ordinary skill in the art to modify the method of Olsson by determining erythrocyte adenylate kinase activity in serum rather than plasma because serum and plasma are

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conventional alternative sample types used in clinical analysis.

Olsson, et al. describe an assay for determining the aging of blood for transfusion purposes by detecting the presence of total adenylate kinase in plasma samples. The samples were obtained from preparations of red blood cells stored in packs for a determined period of time. Since the red blood cell preparations were in a closed and controlled environment, Olsson was measuring only the release of adenylate kinase from erythrocytes as the red blood cell preparations aged. Since the only adenylate kinase released in the red blood cell preparations was from erythrocytes, any adenylate kinase detected in the sample using the method described by Olsson would be erythrocytic in origin. The lack of other origins of adenylate kinase, other than erythrocytic, made it unnecessary for Olsson to specifically distinguish the origin of the adenylate kinase as erythrocytic. Thus, Olsson's use of DAPP did not further distinguish what Olsson already knew - that the adenylate kinase was erythrocytic in origin. In fact, since DAPP strongly inhibits adenylate kinase originating from both erythrocyte and muscle origin, and less strongly from liver (see Szasz, et al. *Clin. Chem.* 22:1806-1811 (1976) which was specifically cited by Olsson), Olsson's use of DAPP to specifically detect erythrocytic adenylate kinase was completely irrelevant since only erythrocyte adenylate kinase was present in the plasma sample, and since DAPP inhibits more than just erythrocytic adenylate kinase. Accordingly, applicants stress that one of skill

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in the art could not and would not have used the method described by Olsson alone or in combination with DAPP to determine whether adenylate kinase originated from erythrocytes, muscle or liver in a serum sample taken from a patient. Since a serum sample taken from a patient is not taken from a closed environment, the sample will contain, unlike the red blood cell samples tested by Olsson, adenylate kinase of erythrocytic, muscle and liver origin. As such, it would have been impossible for one of skill in the art to use the method described by Olsson, alone or in combination with DAPP, to determine whether adenylate kinase detected in a serum sample from a patient originates specifically from erythrocytes, muscle or liver.

Since the method described by Olsson alone or in combination with the use of DAPP could not be used to determine whether adenylate kinase originated from erythrocytes, muscle or liver in a red blood cell sample from a closed environment, it most certainly could not be used, and it would not even be considered by one of skill in the art to use to detect erythrocyte adenylate kinase in a serum sample taken from the human body. Therefore, it would not have been obvious to use the method described by Olsson to diagnose erythrocyte hemolysis, which is a condition whereby a patient's red blood cells are destroyed in the body, in a patient by measuring erythrocyte adenylate kinase.

Further, the methods described by Friedrich, Tsuji and Buth do not teach or suggest a method of specifically

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distinguishing erythrocytic adenylate kinase from adenylate kinase of muscle and liver origin in a serum sample obtained from a patient as taught by the method of the present invention. Tsuji describes visualizing total adenylate kinase, not the determination of the amount or activity of erythrocyte adenylate kinase. Friedrich describes gel electrophoresis of a sample of washed human erythrocytes. However, Friedrich did not distinguish erythrocyte from total adenylate kinase, nor describe the migration position of erythrocyte adenylate kinase that would permit the skilled artisan to reproducibly determine whether erythrocyte adenylate kinase was present in a sample. Buth only shows that NAD can be used to visualize adenylate kinase.

The addition of Matsuura does not remedy the deficiencies of Olsson. Matsuura describe a method for determining the amount of total adenylate kinase in a sample by immunoblot analysis. The anti-adenylate kinase antibody employed in this assay detects all adenylate kinase, regardless of the origin. The method described by Matsura does not teach or suggest a method for determining the specific amount and activity of erythrocytic adenylate kinase in a sample as taught by the present invention. Thus, Matsura could not have been combined with Olsson to arrive at the claimed method.

Accordingly, Olsson taken alone or combined with Friedrich, Tsuji, Buth or Matsuura does not render obvious a method for diagnosing erythrocyte hemolysis in a serum sample obtained from a subject by detecting erythrocyte adenylate kinase in the

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serum sample.

In view of the preceding amendments and remarks, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection set forth in the August 19, 1998 Office Action, and earnestly solicit allowance of the pending claims.

If a telephone interview would further the prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

No fee, other than the \$55.00 fee for a one month extension of time, is deemed necessary in connection with the filing of this Amendment. If any fee, however, is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 01-1785.

Respectfully Submitted,

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